## REMARKS

Claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 are pending in the application. Claims 29, 31, 32, 61 and 64 are presently amended. Specifically, claims 29, 32, 61 and 64 are amended herein to recite "consisting of" rather than "consisting essentially of." As discussed below, use of "consisting of" as a transitional phrase is well established as a claim drafting convention, and accordingly, literal support in the specification need not be shown. Claim 31 is amended to clarify that the nucleotides which comprise the first or second oligonucleotide are ribonucleotides. Support for this amendment can be found in the specification at least at page 18, lines 17-24. Thus, Applicants respectfully assert that no new matter has been introduced by way of the amendments.

The claims stand variously rejected. Each of the rejections is traversed as discussed below.

**Request for consideration of Information Disclosure Statement**

Applicants respectfully request that the documents submitted in the Information Disclosure Statement filed October 12, 2000 be considered by the Examiner and made of record in the present application. Applicants also request that an initialed copy of the corresponding Form PTO-1449 be provided to Applicants in accordance with MPEP §609. For the convenience of the examiner, a copy of the Form PTO-1449 is enclosed.

**Rejections under 35 USC §112, first paragraph**

In the Office Action, claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 are rejected under 35 USC §112, first paragraph, as allegedly containing new matter. The same claims are also rejected because, according to the examiner, the specification does not contain an adequate written description of "just which first and second oligonucleotides meet this [utility] requirement." Applicants traverse the rejections and request reconsideration thereof in light of the following remarks.

New matter

The Examiner appears to argue that because the transitional phrase "consisting essentially of," introduced in Amendments received by the Office on January 14, 2005 and July 22, 2005, does not find literal support in the description or the originally filed claims, use of this phrase constitutes "new matter." However, both the Board of Appeals and the Federal Circuit

have recognized "consisting essentially of" as a *convention* used to signal that the claimed invention necessarily includes the listed ingredients (or method steps) and is open to unspecified ingredients (or method steps) that do not materially affect the basic and novel properties of the invention. *See, e.g., Ex Parte Davis and Tuukkanen*, 80 USPQ 448 (BPAI 1948); *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998).

Applicants do not concede that the present specification fails to describe what constitutes a material change in the basic and novel characteristics of the invention. However, in the interest of advancing prosecution, Applicants have amended the claims herein to recite "consisting of." Applicants respectfully assert that they are permitted to claim their invention using this transitional phrase, which signals that the claim is "closed" to elements other than the limitations that follow the transition. *See, e.g., Ex Parte Grasselli*, 231 USPQ 395 (BPAI 1986). Moreover, the Examiner did not object to use of this transition phrase when it was introduced in prior amendments filed April 28, 2003 and March 1, 2004.

In view of the above, Applicants respectfully request withdrawal of the rejection.

Written Description

The Office Action includes a rejection of claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 for allegedly failing to satisfy the written description requirement. Applicants traverse the rejection.

The Office Action states that "...the specification has not provided such full, clear and concise description of those first and second polynucleotides [sic, oligonucleotides as used in the claimed methods] such that one of skill in the art would be able to recognize those that have utility from those that do not." In other words, the Examiner appears to argue that the specification fails to meet the written description requirement because it fails to describe utility for the oligonucleotides used in the claimed methods.

In contrast, the appropriate inquiry regarding the written description requirement is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

Applicants respectfully assert that the Office Action does not indicate that the Applicants have not shown possession of the claimed invention, alleging instead that Applicants have not

shown utility. Therefore, the Office Action fails to provide any cognizable theory upon which a written description rejection is properly based. To the extent that the Examiner intended the rejection to be made under 35 USC §101, it is addressed below.

Applicants respectfully request that the rejection be withdrawn.

**Utility rejection under 35 USC §§ 101 and 112**

In the Office Action, claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 are rejected under 35 USC §101, because, according to the Examiner, "the claimed invention is not supported by either a specific and substantial utility or a well established utility." The Office Action also indicates that the claims are also rejected for lacking enablement under 35 USC §112, first paragraph for allegedly failing to teach "how to use." The rejections are traversed.

The Office Action states that the utility requirement can be satisfied "either directly from the method [or] downstream therefrom." The Office Action further alleges that "satisfaction of the utility requirement is not achieved by simply labeling and/or detecting any nucleic acid as not all nucleic acids have utility." No supporting legal authority is provided for this allegation.

To properly reject a claimed invention under 35 USC §101, the Examiner must (a) make a *prima facie* showing that the claimed invention lacks utility, and (b) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. MPEP 2107.02 (IV). Moreover, the claimed invention must be the focus of the assessment of whether Applicants have satisfied the utility requirement. MPEP 2107.02 (I). Thus, the Examiner's unsupported allegation that utility must be shown, not for the method claimed, but for nucleic acids that might be labeled according to the claimed methods, is not correct.

Applicants' claims are directed to methods of labeling oligonucleotides. As taught by the specification, e.g., at page 5, lines 1-7, such methods are useful in generating high specific activity probes which can be used by the researcher to, e.g., identify the presence of a specific nucleic acid, as discussed in the specification, e.g., at page 1. Accordingly, the claimed methods clearly have specific and substantial utility.

The Examiner is directed to MPEP 2107.01, which states that "many research tools such as gas chromatographs, screening assays and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)." Like the exemplified "research tools," Applicants respectfully assert that the presently claimed methods are similarly "useful in analyzing compounds," i.e., nucleic acid sequences, and therefore, also, have a clear, specific, and unquestionable utility.

In view of the above, withdrawal of the rejections under 35 USC §101 and 35 USC §112 is respectfully requested.

**Rejection under 35 USC §112, 2nd paragraph**

In the Office Action, claim 30 is rejected under 35 USC §112, second paragraph.

In accordance with the Examiner's suggestion, Applicants have amended claim 30 to clarify what was clearly intended by Applicants, i.e., that the nucleotides which comprise the first or second oligonucleotide are ribonucleotides.

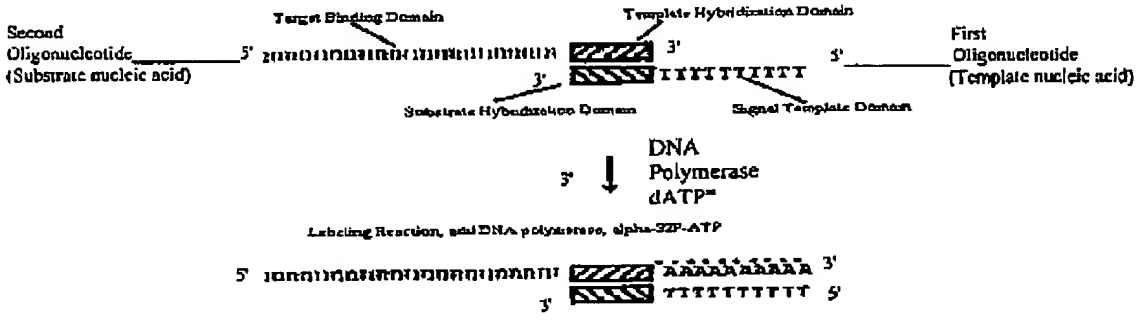
Accordingly, withdrawal of the rejection is respectfully requested.

**Rejection under 35 USC §103(a)**

In the Office Action, claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 are rejected as obvious under 35 USC §103(a) over Shuber (U.S. Patent 5,882,856), in view of Khan (U.S. Patent 6,248,568), Grossman (U.S. Patent 5,989,871) and Brown (WO 93/05175). The rejection is respectfully traversed.

As a preliminary matter, Applicants have apparently previously persuaded the Examiner that the presently claimed invention is not obvious over the combination of Shuber and Eyler, as evidenced by the withdrawal of the rejection in the Non-final Action mailed April 20, 2005. Applicants respectfully submit that the presently applied secondary references no more cure the deficiencies of the primary reference than does Eyler. As explained below, the presently cited references, whether alone or in combination, fail to teach all of the claim limitations.

In one aspect, the invention includes methods of labeling the 3' end of an oligonucleotide to produce a detectably labeled oligonucleotide probe having a high specific activity. As diagrammed below, the method involves hybridizing two oligonucleotides together through short hybridization domains of about 5 to about 20 nucleotides:



The first oligonucleotide or "Template Nucleic Acid," which consists of a Substrate Hybridization Domain of about 5 to about 20 nucleotides at or near its 3' end adjoining a 5' Signal Template Domain of about 5 to about 100 nucleotides, is hybridized to the second oligonucleotide (referred to as "Substrate Nucleic Acid" in the application), which comprises a Template Hybridization Domain consisting of about 5 to about 20 nucleotides at or near its 3' end, adjoining a heterologous 5' Target Binding Domain, through base pairing between five or more nucleotides of their respective hybridization domains. The first oligonucleotide, or Template Nucleic Acid, has a sequence that is heterologous to that of the Target Binding Domain, i.e., it does not follow the Target Binding Domain in its native context. (Page 10, lines 17-21). Following hybridization, a DNA polymerase catalyzes the addition of detectably labeled nucleotides to the 3' end of the second oligonucleotide, or Substrate Nucleic Acid, to form a detectably labeled oligonucleotide probe that can be used to detect sequences complementary to the 5' Target Binding Domain. The labeled oligonucleotide Probe thus produced comprises, from 5' to 3', a Target Binding Domain, a Template Hybridization Domain, and a labeled Signal Domain.

The Examiner asserted that Shuber discloses the use of a chimeric primer configured as 5' -XY-3', with the "X" domain comprising a sequence that does not hybridize to the target sequence and the "Y" domain comprising a sequence contained within or flanking the target sequence or its complement. The Examiner therefore concluded that the "X" domain meets the limitations of applicants' Signal Template Domain and the "Y" domain meets the limitations of applicants' Substrate Hybridization Domain of the first oligonucleotide. The Examiner further concluded that Shuber's "target sequence" meets the limitations of applicant's second nucleic acid sequence. Applicants respectfully disagree that the constructs described by Shuber meet the limitations of the oligonucleotides used in Applicants' claimed methods.

In contrast to the claimed invention, Shuber discloses a method of simultaneous PCR amplification of multiple target DNA sequences, each of which requires a DNA primer pair. According to Shuber et al., the primers described therein hybridize to a genomic target sequence through a 3' sequence ("Y") of the primer that is complementary to the target sequence and facilitates amplification of the target sequence or sequence flanking the target sequence by 3' extension of the primer. In contrast, the first oligonucelotide used in the presently claimed methods is a universal template in that its interaction with the second oligonucleotide occurs through complementary hybridization domains with sequences heterologous to the target sequence.

Contrary to the Examiner's assertion that the first oligonucleotide of the presently claimed invention has the same configuration as that used in the methods of Shuber et al., the 3' end of the first oligonucleotide (Template Nucleic Acid) of independent claims 29 and 64 (and accordingly, the dependent claims) does not comprise "a sequence contained within or flanking the target sequence or its complement," as in Shuber. The Examiner appears to suggest that because the 3' Substrate Hybridization Domain is complementary to the Template Hybridization Domain, and the Template Hybridization Domain flanks the Target Binding Domain, Shuber et al. teaches the first oligonucleotide. However, the present claims require that the Substrate Hybridization Domain of the first oligonucleotide is complementary to a sequence that is heterologous to the target sequence (page 10, lines 17-21).

Moreover, the target sequence of Shuber, which the Examiner has alleged teaches the limitations of the second oligonucleotide used in the presently claimed methods, will not be extended in the presence of labeled nucleotides to result in a labeled Signal Domain complementary to the 5' Signal Template Domain of the first oligonucleotide to form a labeled oligonucleotide probe.

Applicants submit that neither the first nor second oligonucleotide of claim 29 would be capable of performing the method of Shuber et al. If one attempted to use the first oligonucleotide of the present claims, which is heterologous to the target sequence, no hybridization, and therefore, no amplification, would occur. As for the second oligonucleotide, the 5' end of the primer would hybridize to the target, but the 3' end would not. Therefore, a DNA polymerase would be unable to catalyze the amplification of the target sequence to produce PCR products.

Similarly, substitution of either the first or second oligonucleotide of the claims for the primer or target disclosed in Shuber et al. would not result in the formation of a labeled oligonucleotide having, from 5' to 3', a Target Domain adjoined to a Template Hybridization Domain heterologous to the target, adjoined to a labeled Signal Domain, as required by step (b) of claim 29.

As the Examiner acknowledged, Shuber et al. does not teach or suggest incorporation of labeled nucleotides. Applicants respectfully submit that Shuber et al. does not disclose incorporation of labeled nucleotides precisely because the method described is intended to produce multiple copies of target sequences through PCR amplification for use in subsequent analysis, not to make a labeled oligonucleotide probe according to the present invention. Thus, contrary to the assertions in the Office Action, one of skill in the art would find no motivation in Shuber et al. to combine its teachings with Khan et al., which is said to "disclose the

incorporation of labeled nucleotides into primer extension products," or Grossman et al., which is said to disclose "the use of a detectable nucleotide."

Grossman et al. is also cited as disclosing "the generation of homopolymeric tails." However, Grossman et al. is directed to a method of altering the ratio of charge/translational frictional drag of binding polymers that would otherwise have substantially identical ratios of charge/translational frictional drag, such that a plurality of sequences may be separated electrophoretically. Col. 3, lines 10-16. The methods described in Grossman provide for modification of probes after they have bound to their target sequence by attaching reporter groups at the 3' end of the bound probe. Cols. 3-4. As taught by Grossman, methods of modifying the bound probes may include "homopolymer tailing." Col. 19, lines 34-44. In the context of the methods described in Grossman, "homopolymer tailing" refers to the use of terminal transferase in the presence of dNTPs to add residues to the 3' hydroxyl terminus of the bound probes, and does not refer to the template-dependent polymerase-mediated addition of the Signal Domain as in step (b) of present claim 29 and its dependent claims. Thus, Grossman et al. does not cure the deficiencies of Shuber.

The Office Action states that Brown et al. disclose the use of 2,6-diaminopurine in oligonucleotides and their use in primer extension reactions. The Office Action, does not, however, explain why one of skill in the art would combine Brown et al. with Shuber et al., Khan et al. and/or Grossman et al. or to modify any of these disclosures. Even if Brown were fortuitously combined with these references, as explained above, all elements of the presently claimed methods are not taught or suggested.

Accordingly, Applicants respectfully request withdrawal of the rejection of under 35 USC §103(a).

**Request for Supervisory Patent Examiner Review**

Applicants respectfully direct the Examiner's attention to MPEP 707.02, which states:

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>
> The supervisory patent examiners are expected to personally check on the pendency of every application which is up for the third or subsequent Office action with a view to finally concluding its prosecution.
>
> Any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort should be made to terminate its prosecution. ***

Applicants note that the present application has been pending well over five years, and has been the subject of no fewer than seven Office Actions, with all but one of them being Non-final. Three Non-final actions have issued since an RCE was filed by Applicants in March of 2004.

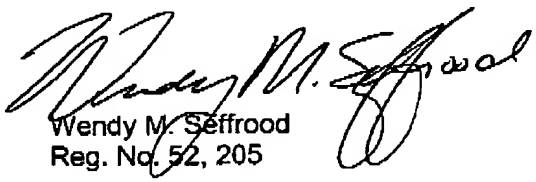
The present Non-final action includes new matter, written description, indefiniteness and utility rejections, each of which the Examiner has raised for the first time and each of which cannot be said to have been necessitated by amendment. The present Non-final action also includes an obviousness rejection which was not earlier presented, although the individual references were previously applied in different combinations in rejections that were later withdrawn. This sort of "piecemeal examination" is clearly prohibited by MPEP 707.07(g).

The history of the application before the present Examiner amply demonstrates that prosecution is proceeding "with a view to finally concluding its prosecution." In the event that the Examiner does not withdraw all pending rejections, the Examiner is respectfully requested to present the application to the Examiner's Supervisor for review and guidance. Failing all else, the Examiner is requested to issue a Final action so that Applicants may appeal the rejections.

## CONCLUSION

In view of the foregoing, reconsideration and allowance of claims 29-33, 35, 37-41, 43-48, 55, 56 and 58-64 is respectfully requested. The Examiner is invited to contact the undersigned by telephone at the Examiner's convenience should any issues remain with respect to the Application.

Respectfully submitted,



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